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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/058,546	04/10/1998	WALTER H. GUNZBURG	GSF98-02A	7592

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/05/2003

23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/058,546	GUNZBURG ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18-64* is/are pending in the application.

4a) Of the above claim(s) *1-12,18,24,25,29,30,33-38,44,49,54 and 55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-16, 19-23, 26-28, 31, 32, 39-43, 45-48, 50-53 and 56-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other.

DETAILED ACTION

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1632.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12-30-02, paper number 21, has been entered.

Election/Restriction

This application contains claims 1-12, 18, 24, 25, 29, 30, 33-38, 44, 49, 54 and 55 drawn to an invention nonelected with traverse in Paper No. 17. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Applicants argue the claims do not encompass antisense. Applicants argument is not persuasive because claims 5-7, 18, 24 explicitly require antisense. Therefore, the restriction is maintained.

Claims 62-64 have been added. Claims 13-16, 19-23, 26-28, 31, 32, 39-43, 45-48, 50-53 and 56-64 are under consideration in the instant office action.

Applicant's arguments filed 12-30-02, paper number 22, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

Claim 14 should be changed from "The producer cell of Claim 13" to --The isolated producer cell of claim 13-- to parallel the claim language in claim 13 (directed to an "isolated producer cell").

Claim Rejections - 35 USC § 112

1. Claims 15, 16, 20-23, 27, 28, 31, 32, 41, 42, 46, 47, 51, 52 and 56-61 remain rejected and 62-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating restenosis or cancer by contacting the site of restenosis or cancer with a retrovirus encoding SDI-1 resulting in a therapeutic effect, does not reasonably provide enablement for using any mode of delivery as broadly claimed, using producer cells or capsules to treat disease, or using analogues or fragments of SDI-1 to treat disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

Claims 21, 26, 27, 32, 59 and 63 are directed toward treating disease using a retrovirus, a producer cell that makes a retrovirus or an encapsulated producer cell that makes a retrovirus encoding SDI-1. The claims are not limited to any route of administration and, therefore, encompass any route of administration. Claim 31 is limited to injecting a retroviral particle "nearby or at the site of the tumor" but is not limited to treating tumors, and the metes and bounds of "nearby" are unclear (see 112/2nd).

The specification does not enable treating disease, specifically restenosis or cancer, using any route of administration as broadly claimed. Crystal (1995, Science, Vol. 270, page 404-410; page 409) and Feldman (1995, Fundamental & Clin. Pharm., Vol. 9, pages 8-16), both of record, taught the combination of vector and mode of delivery for gene therapy required to target the desired tissue and provide adequate expression of a protein such that a desired effect was obtained was unpredictable. The specification taught administering a retrovirus encoding SDI-1 to tumor cells *in vitro* inhibited hyperproliferation (pg 27, lines 1-7).

Since the time of filing, Nabel (US Patent 5,863,904) taught administering an adenovirus encoding SDI-1 to a site of rustenosis *in vivo* treated the disease (col. 8, line 10) and to hyperproliferating smooth muscle cells or tumor cell *in vitro* inhibited hyperproliferation (col. 8, lines 1-3; col. 10, col. 22-26). Nabel taught the adenovirus could be replaced with a retrovirus for delivery of SDI-1 (col. 3, line 10; col. 4, line 60). Nabel was not available to the public until Jan. 26, 1999.

The art at the time of filing did not teach how to treat diseases responsive to the antiproliferative activity of SDI-1 using a retrovirus encoding SDI-1 other than by administering the virus directly to the site of disease. The specification does not correlate administering the virus directly to the site of disease with other modes of delivery to enable any mode of delivery as broadly claimed. Given the unpredictability in the art taken with the teachings in the specification and the post filing evidence of Nabel, it would have required one of skill undue experimentation to determine how to deliver a retrovirus encoding SDI-1 to treat disease other than by direct injection to the site of disease.

Claims 15, 16, 20-23, 41, 42, 46, 47, 51, 52, 56-61, 63 and 64 encompass capsules comprising producer cells, and methods of using capsules or producer cells to treat disease. The only disclosed use for the capsules comprising producer cells are for therapy *in vivo*. Applicants have not pointed to another purpose for the capsule.

The specification does not provide adequate guidance to use producer cells or capsules comprising producer cells to treat disease. The art at the time of filing did not teach how to administer a producer cell or an encapsulated producer cell making a retrovirus to treat disease. The art at the time of filing and the specification do not teach that the producer cells or capsules produce adequate amounts of retrovirus such that a therapeutic effect could be obtained. Therefore, the specification does not provide adequate guidance regarding the site of administration of producer cells or capsules or the secretion of retrovirus from the producer cells or capsules that correlates to the amount of retrovirus directly injected to the site of disease that is

therapeutic. Given the unpredictability in the art taken with the guidance provided in the specification about how to administer producer cells or capsule to treat disease, it would require one of skill undue experimentation to determine how to administer producer cells or capsules to treat disease.

Applicants point to references that do not teach using capsules to treat disease; however, applicants conclude that producer cells can be used to treat disease (pg 6, last 6 lines of second para.). Applicants argument is flawed. No teachings in the art provide guidance for one of skill to obtain therapeutic levels of secretion of retrovirus using producer cells or capsules *in vivo*. No such teachings are found in the specification.

Applicants argue Crystal and Feldman do not teach that the combination of vector and mode of delivery for gene therapy required to target the desired tissue and provide adequate expression of a protein was unpredictable (pg 6, last para.). Applicants quote Crystal which concludes gene therapy is feasible. Applicants state Feldman reviews clinical trials and new avenues for protection for restenosis. Applicants cite Nabel which teaches administering a retrovirus encoding SDI-1 to treat rustenosis. Overall, applicants argument that Crystal and Feldman do not establish the unpredictability in the art are not persuasive. Just because Crystal believed gene therapy was feasible does not negate the fact that Crystal also thought that the parameters required to obtain a therapeutic effect using gene therapy were unpredictable. While Feldman reviewed the field of gene therapy for rustenosis, Feldman considered the parameters required to treat disease using gene therapy unpredictable for reasons of record. Feldman (1995)

did not have access to the results of Nabel (US 5,863,904) which was not published until 1-26-99 and could not be used by one of skill at the time of filing.

Claim 15 encompasses a capsule comprising a producer cell transfected with a retroviral vector encoding a functional analogue or fragment of SDI-1. Claims 46, 47, 51 and 52 encompass capsules comprising packaging cell lines that make retroviral particles encoding amino acids 1-71 or 42-58 of human SDI-1. Claim 63 encompasses a method treating disease using a capsule comprising a producer cell transfected with a retroviral vector encoding a functional analogue or fragment of SDI-1. Claims 15, 46, 47, 51, 52 remain rejected and 63 is rejected for reasons of record regarding functional fragments of SDI-1 capable of treating disease.

Applicants argue they have provided an assay for determining fragments, i.e. the *in vitro* assay for the number of cells in G_0/G_1. But applicants have not provided the amount of inhibition required for a fragment *in vitro* that indicates the fragment is capable of treating disease. Applicants have not provided any data indicating any fragment has the same function as full length SDI-1 such an assay. Without such guidance, it would require one of skill undue experimentation to determine any fragment or analogue of SDI-1 capable of treating disease *in vivo*. It would require one of skill undue experimentation to determine whether a retrovirus encoding amino acids 1-71 or 42-58 of human SDI-1 using any route of administration as broadly claimed would have a therapeutic effect. It cannot be determined whether amino acids 1-71 and

42-58 of the SDI-1 protein as described by El-Deiry, Harper or Xiong have the same antiproliferative activity of full length SDI-1. Therefore, applicants argument is not persuasive.

2. Claims 31, 32 and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 is indefinite because "the site of the tumor" lacks antecedent basis in claim 31. The individual in parent claim 28 may have rustenosis and therefore, may not have a tumor. Or perhaps the applicants consider hyperproliferating smooth muscle cells found in rustenosis a "tumor." The individual in parent claim 28 may have cancer, but the cancer may be in remission; therefore, the individual may not have a tumor. Overall, it is unclear how the limitation in claim 31 further limits claim 28. Clarification is required.

Claim 31 is indefinite because it does not clearly refer back to the method of the parent claim. "A method according to claim 28" should be --The method according to claim 28--.

Claims 31 and 63 are indefinite because the metes and bounds of injection "nearby... ...the site of tumor" is unclear. The term "nearby" is not defined in the specification and does not have an art recognized meaning; therefore, one of skill would not be able to determine when an injection was no longer "nearby" the site of the tumor. How "near" is "nearby?"

Claim 32 is indefinite because the step of "administering a producer cell line according to Claim 13" does not clearly set forth to what the cell line is being administered. It is unclear if the

cells are administered to cell *in vitro* which is then used to treat the disorder or to a capsule or to another individual who then administers chemotherapy to the individual. As such, the metes and bounds of the claim are unclear.

Claim 32 is indefinite because it does not clearly refer back to the product of the parent claim. The phrase "a producer cell line according to claim 13" should be --the producer cell line according to claim 13--.

Claim 63 is indefinite because the phrase "an encapsulated packaging cell line comprising encapsulated cells having a core containing packaging cells harboring" is unclear. The structure of what is being implanted cannot be determined. It is unclear if a core with producer cells and encapsulated cells is implanted or if a core and producer cells are implanted, i.e. it is unclear whether the producer cells and encapsulated cells differ, and if so how? It is also unclear whether cells within the core differ from cells within a capsule or encapsulated cells. Clarification is required.

Claim Rejections - 35 USC § 103

3. Claims 13, 14, 19, 26-28, 31, 32, 39, 40, 45, 48, 50 and 53 remain rejected and claim 62 is rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (1989, Biotechniques, Vol. 7, pages 980-990) or Price (1987, PNAS, USA, Vol. 84, pages 156-160) in view of Nabel (US Patent 5,863,904, Jan 26, 1999) for reasons of record.

Miller and Price taught stably transfected packaging cells producing retroviral particles (pg 981, col. 1, col. 3 and pg 156, col. 2, line 18, respectively). The packaging cells are suspended in culture media which is a "carrier" as claimed. Miller and Price did not teach the retroviral particles encoded SDI-1 or treating restenosis using retroviral particles encoding SDI-1. However, Nabel taught retroviral particles encoding SDI-1 and injecting viral particles into a patient to treat restenosis (see abstract; col. 3, line 10; col. 4, line 60; claim 1; col. 3, line 10). The SDI-1 protein of Nabel encodes full length SDI-1; therefore, the retroviral particle of Nabel encodes full length SDI-1 which comprises amino acids 1-71 and 42-58 of SDI-1 as claimed. The limitation of a pharmaceutical composition is an intended use and does not bear patentable weight in considering the art.

Thus, it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to make a stably transfected packaging cell that produces retroviral particles as taught by Miller or Price to make retroviral particles encoding SDI-1 as taught by Nabel. One of ordinary skill would have been motivated to make retroviral particles encoding SDI-1 using the methods taught by Miller or Price because Miller and Price state the retroviral particles can be used *in vivo* (page 989, last sentence and page 157, column 1, fourth paragraph, respectively) and because Nabel taught making and using retroviral particles encoding SDI-1 to treat restenosis (col. 3, line 10).

The discussion on pg 10, lines 3-21, comparing DNA and RNA viruses, is unclear. It is especially unclear what is being emphasized in bold faced type. It is unclear how the difference

between DNA and RNA viruses indicates the combined teachings are not enabling or are missing an element of the claim.

Applicants arguments on pg 10, line 22, through pg 11, line 4, appear to be that Nabel did not teach using retrovirus for delivery of SDI-1. Applicants argument is not persuasive. While Nabel taught a preferred vector for delivering DNA encoding SDI-1 was an adenoviral vector, Nabel also taught a retroviral vector could be used, preferably with impaired ability to replicate (col. 3, line 10) and taught adjusting the titer injected when using retrovirus (col. 4, line 60). Given the teachings of Miller or Price who explicitly teach how to make retroviral particles from packaging cell lines taken with the teachings of Nabel, the combined teachings of Miller or Price taken with Nabel provides adequate guidance for a packaging cell line that makes retroviral particles encoding SDI-1 or delivering a retroviral particle encoding SDI-1 made from a packaging cell line as claimed.

Applicants state Miller and Price do not teach what is lacking in the Nabel reference but do not state what Miller and Price are lacking (pg 11, line 5). Miller and Price each teach how to make a retroviral particle encoding a protein using a packaging cell (which appears to be what applicants consider the deficiency of Nabel according to the arguments on pg 9-11). Therefore, applicants' argument is not persuasive.

Applicants argue there would be no motivation to combine Miller or Price with Nabel because one of skill would not expect a stably transfected producer cell line that makes a retroviral genome encoding SDI-1 could be produced.

a. Motivation to combine the references was provided by Nabel who suggested using a retrovirus to deliver DNA encoding SDI-1 (which can only be made using a retroviral packaging cell line).

b. Nabel taught making adenovirus encoding SDI-1 using producer cell line 293 indicating producer cells expressing SDI-1 are still capable of producing virus (col. 6, lines 21-42; see line 32 which teaches making adenovirus in 293, an adenovirus producer cell line).

c. Regarding any "reasonable expectation of success", applicants' argument is also not persuasive. The "reasonable expectation of success" argument is based on that fact that SDI-1 was known in the art at the time to inhibit cell proliferation and DNA synthesis. Therefore, transfecting packaging cells with a vector encoding SDI-1 would prevent cell division and the production of "stably transfected" retroviral packaging cells. However, Miller and Price obtained stably transfected packaging cells that produce retroviral particles. In addition, Nakanishi of record (1995, EMBO, Vol. 14, pg 555-563) taught stably transfecting numerous cells with a vector encoding p21 (another name for SDI-1) that survived and replicated for at least 72 hours (pg 562, col. 2, "transfection and determination of DNA synthesis inhibitory activity"). Just because SDI-1 inhibits proliferation or DNA synthesis does not mean SDI-1 prevents proliferation and DNA synthesis. Given the suggestion of Nabel (who is one of ordinary skill in the art at the time of filing) to make retroviral particles encoding SDI-1 taken with the teachings in the art at the time of filing, one of ordinary skill would not have reasonable concluded that retroviral particles encoding SDI-1 could not be produced using a retroviral packaging cell line.

or that retroviral packaging cells could not be "stably transfected" as claimed. It is noted that the transfected producer cells of claim 13 do not require that the cells have normal proliferation or DNA synthesis. Therefore, one of ordinary skill would have had a "reasonable expectation of success" in obtaining a "stably transfected" producer cell line that made retroviral particles encoding SDI-1 as claimed.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER